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Genetic Architecture of Smoking Behavior: A Study of Finnish Adult Twins

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Both genetic and environmental factors affect smoking initiation and maintenance, but less is known about the genetic architecture of various other smoking-related behaviors. The aim of this study is to examine the genetic architecture of smoking behavior in a large twin cohort. Questionnaires with an extensive smoking history section were mailed to same-sex adult twins of the Finnish twin cohort. The final study population included 2923 monozygotic and 6018 dizygotic twin pairs aged 24 to 88 years. Two-stage bivariate genetic modeling of age at initiation with amount smoked (less than 20 cigarettes per day vs. 20 or more) and age at initiation with smoking cessation was done by using the Mx statistical package. For men the heritability estimate for age at initiation was .59 (95% confidence interval [CI] .49–.69), for amount smoked .54 (95% CI .45–.62) and for smoking cessation .58 (95% CI .50–.65). For women the heritability estimates were .36 (95% CI .28–.43), .61 (95% CI .46–.70) and .50 (95% CI .39–.60), respectively. The genetic correlations between age at initiation and amount smoked or smoking cessation were at most .22 in magnitude, indicating that genetic influences in age at initiation accounted for at most about 4% of the genetic factors in amount smoked or in cessation. Genetic factors are important in amount smoked and smoking cessation and they are largely independent of genetic influences on age at initiation. This has implications for defining phenotypes in searches for genes underlying smoking behaviors.

The genetic architecture of many features of smoking behavior based on twin and family studies is fairly well characterized (Li et al., 2003). The results, however, vary. Some studies have suggested that there is a strong genetic contribution to variation in smoking behavior (Edwards et al., 1995; Heath et al., 1993; Kaprio et al., 1981; Kendler et al., 1999), but there are also studies which have found little evidence of a genetic effect (Heath et al., 1993; Heath et al., 1999). Most of the studies on the genetic architecture of smoking behavior have examined smoking initiation and smoking cessation, while quantitative genetic studies on other smoking behaviors and related traits are fewer.

Earlier studies have revealed a substantial genetic contribution to risk of smoking initiation, and the heritability estimates in these studies range from .32 to .78 (Edwards et al., 1995; Heath et al., 1993; Heath et al., 1999; Heath et al., 1998; Kendler et al., 1999; Madden et al., 2004; True et al., 1997; Vink, 2004). This variation is not surprising, taking into account that the role of genetic factors probably varies with time and place (Kendler et al., 1999). A meta-analysis by Li et al. (2003) showed that on average heritability of smoking initiation appears to be higher in adult women (55%) than in adult men (37%) as it did in studies of Madden et al. (1999) and Heath et al. (2002).

Another well studied aspect of smoking behavior is smoking cessation versus persistence among regular smokers. In the previous studies, heritability estimates of smoking cessation have varied from .11 to .74 (Heath et al., 1993; Heath et al., 1999; Heath et al., 1998; Heath et al., 2002; Kaprio et al., 1981; Kendler et al., 2000; Madden et al., 1999; Medlund et al., 1977; True et al., 1997). However, only a few of these studies include both men and women from the same population. Genetic effects on smoking cessation seem to be higher among men than among women (Li et al., 2003; Madden et al., 2004; Maes et al., 2004).

The amount smoked has been studied both as a trait in itself and as a proxy measure for nicotine dependence. Analyses of amount smoked have been done mostly among men (Carmelli et al., 1990; Swan et al., 1996; Swan et al., 1997; Swan et al., 1990). Smoked cigarettes per day has been examined in three ways: highest number of cigarettes ever smoked per day (Carmelli et al., 1990; Swan et al., 1996; Swan et al., 1990; among men, $h^2 = .52$ to $.56$), as a dichotomy of light or heavy smokers (Swan et al., 1997; among men, $h^2 = .49$) or the number of cigarettes smoked per day as a categorical variable (Vink et al., 2004; among both sexes, $h^2 = .51$). Nicotine dependence is determined either by the Fagerström test

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for nicotine dependence (Heatherton et al., 1991) or the criteria of *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; DSM-IV; American Psychiatric Association, 1994) and DSM-III-R (3rd ed., rev.; American Psychiatric Association, 1987) nicotine dependence. In these studies, heritability estimates in adults have varied from .60 among men (True et al., 1999) to .72 among women (Kendler et al., 1999) and .56 among both men and women (Lessov et al., 2004).

Many of the previous studies have examined only one smoking behavioral factor at a time. Bivariate analyses have been conducted for initiation and dependence (Kendler et al., 1999), initiation and smoking persistence (Madden et al., 1999), and a trivariate analysis has been conducted for initiation, regular tobacco use and nicotine dependence (Maes et al., 2004). Anyhow, we lack studies comparing genetic influences in age at initiation, amount smoked per day and smoking cessation in the same study. Thus, the previous quantitative genetic studies on smoking behavior give little information on the mutual associations between these different smoking behavioral factors. For example, it has been found that persons who start to smoke in young age smoke also, on average, more cigarettes per day than those who start to smoke later (Broms et al., 2004; Jarvis, 2004). However, it is not known whether this trait correlation is because of common genetic factors, common environment, or direct associations between age at initiation and amount smoked per day. Another problem in the previous studies on the genetic architecture of smoking behavior is that only a few studies have included both smokers and nonsmokers (Heath et al., 2002; Kendler et al., 1999; Maes et al., 2004), whereas others have been targeted to concordant smoking pairs only. Heath et al. (2002) have pointed out that if the same genetic and environmental factors that determine variation in risk of dependence among users also determine risk of initiation, then excluding never smokers, that is, discordant pairs and concordant never-smoker pairs, from analyses, discards genetic information. In analyses of twin data, it will also lead to biased estimates of genetic and environmental effects on risk of dependence.

The aim of this study is to examine the genetic architecture of smoking behavior by using a large Finnish data set of adult male and female twins. We address the following specific research questions: (1) What is the effect of genetic and environmental factors on age at initiation, smoked cigarettes per day and smoking cessation? and (2) Are there same genetic and environmental factors behind these phenotypes?

Materials and Methods

The Older Finnish Twin Cohort was established to examine the genetic, environmental, and psychosocial determinants of chronic diseases and health behaviors (Kaprio & Koskenvuo, 2002), and includes data on same-sex twin pairs born before 1958 with both members alive in 1967. The study was accepted by the Ethical Committee of the University of Helsinki and followed the rules and principles of the Helsinki Declaration. The first questionnaire survey was carried out in 1975. The second questionnaire was sent in the autumn of 1981 to all twins then alive in the cohort, including ones nonrespondent in 1975. Earlier heritability estimates of smoking behaviors from the 1975 questionnaire have been reported (Heath et al., 1998; Kaprio et al., 1981; Madden et al., 1999; Madden et al., 2004). This is the first time we report heritability estimates based on the 1981 questionnaire.

In the 1981 survey, the number of respondents was 24,053 and the response rate was 84%. Both twins responded from 9880 pairs, who formed the basic study population, and were aged 23 up to 88 years (mean age 40 years).

Zygosity was determined by asking two questions about the similarity of appearance at school age. The reliability of the questionnaire method for zygosity was assessed by using 11 blood markers in a subsample of 104 twin pairs classified as monozygous (MZ) or dizygous (DZ; Sarna et al., 1978). The agreement between the blood tests and the questionnaire was 100%. It was estimated that the probability of misclassification based on the questionnaire method was 1.7%.

We excluded from the analyses the pairs with unknown zygosity (866 pairs) and the pairs lacking smoking cessation information on either twin (73 pairs). The final study population included 2923 MZ and 6018 DZ twin pairs. The high DZ to MZ ratio reflects the high rate of DZ twinning in the first half of the 20th century in Finland.

In the questionnaire, current smokers were classified as persons who had smoked at least 5 to 10 packs of cigarettes over their lifetime and who were smoking daily or almost daily at the time of the study (Kaprio & Koskenvuo, 1988; Broms et al., 2004). Two questions were asked: 'Have you ever smoked more than 5 to 10 packs of cigarettes in your lifetime?' Those responding positively were then asked: 'Do you smoke or have you smoked cigarettes regularly, daily, or almost daily during your lifetime?' Regular smokers were classified for smoking cessation as follows: former smokers and current smokers. Never and occasional smokers were considered to have missing data for the smoking cessation item.

Age at initiation of smoking was asked by the question: 'What age were you when you started to smoke regularly?' (Broms et al., 2004). Smokers were classified as early starters if they reported to start to smoke regularly when they were 18 years old or younger and as late starters if they had reported to start to smoke regularly when they were older than 18 years. Never smokers and occasional smokers were placed in the category of no initiation. Thus, there were three categories of the age at initiation variable. The correlation between age at initiation as reported in health questionnaire surveys conducted in 1975 and 1981 was .84 among all smokers, with no variation by smoking status or sex.

Smokers were asked a question about the amount of smoking as follows: 'How many cigarettes do you smoke daily on average?' The response alternatives were: none, less than 5, 5–9, 10–14, 15–19, 20–24, 25–39, and more than 40. In the questionnaire, the question for former smokers was same as above but it was in the past tense. We classified amount of smoked cigarettes per day in two categories as follows: less than 20 cigarettes, that is, less than one pack, and 20 cigarettes or more, that is, one pack or more.

The data were analyzed using quantitative genetic methods based on linear structural modeling. Twin modeling is based on the assumption that MZ twins are genetically identical whereas DZ twins share on average 50% of their segregating genes. Thus, a greater similarity for MZ twins compared with DZ twins gives support to the hypothesis that genetic transmission is a component of importance, under the assumption that MZ and DZ share to the same extent their trait-relevant environmental experiences (Boomsma et al., 2002; Neale et al., 2003; Posthuma et al., 2003). Environmental factors are divided into factors shared by a twin pair (shared environment) and factors unique to each twin individual (unique environmental effects), which also includes measurement error. The correlations for the shared environmental factors are 1 and for unique environmental factors 0 within both MZ and DZ twin pairs. The Mx statistical package (Neale et al., 2003) was used to estimate the proportion of trait variance accounted for by additive genetic factors (A), by shared environmental factors (C) and by factors not shared (unique) with the co-twins (E). The ACE model was selected as a starting point of the modeling based on twin correlations. First, a full model was fitted including ACE effects for both age at initiation and amount smoked and the correlations between the genetic and environmental components affecting these two phenotypes. Second, we studied the statistical significance of each component of the base model by fixing them zero to find the most parsimonious model, which was used in the future modeling.

We first used univariate modeling and then the two-stage modeling approach developed by Heath et al. (2002). Two-stage modeling gives results of genetic and environmental variation and correlation of two variables in the situation of structural missing data in one variable. This model permits including the information from never smokers to the analysis. We based our analyses on the Mx scripts given by Heath et al. (2002). All models were fitted using Mx software, using the option for ordinal data-analysis (Neale et al., 2003).

Results

Descriptive Statistics

Table 1 summarizes the distribution of smoking behavior data in the Older Finnish Twin Cohort in 1981. Forty-six per cent of all participants were men and 54% women. Among men 28% were former smokers and 37% current smokers whereas in women the proportions were 15% and 21%, respectively. Approximately equal amounts of subjects had started smoking early or late, and there were no major differences in these proportions by smoking cessation or sex. The number of smoked cigarettes per day was higher among men than among women. The great majority (73%) of smokers smoked less than 20 cigarettes per day. The proportion of those who smoked 20 or more cigarettes was greater among men and current smokers compared with women and former smokers.

Table 1

Numbers and Percentages by Smoking Cessation Age at Initiation and Amount Smoked per Day in the 1981 Questionnaire of Finnish Adult Twins Born Before 1958

Smoking cessation	Men		Women	
	N	%	*N*	%
Never smoked regularly	3229	35.6	6889	64.4
Former smoker	2513	27.8	1615	15.1
Current smoker	3320	36.6	2194	20.5
Total number	9062		10,698	
Total percentage	45.9		54.1	
Smoking cessation and early or late age at initiation				
Never smoked regularly	3229	35.6	6889	64.4
Former smoker, started at age 18 or earlier	1453	16.0	921	8.6
Former smoker, started older than 18	1060	11.7	694	6.5
Current smoker, started at age 18 or earlier	2117	23.4	1184	11.1
Current smoker, started older than 18	1203	13.3	1010	9.4
Total	9062		10,698	
Smoking cessation and smoked less than 20 cigarettes or 20 and more cigarettes per day				
Never smoked regularly	3229	35.6	6889	64.4
Former smoker, smoked less than 20 cigarettes per day	1665	18.4	1424	13.3
Former smoker, smoked 20 cigarettes or more per day	848	9.4	191	1.8
Current smoker, smoked less than 20 cigarettes per day	1988	21.9	1822	17.0
Current smoker, smoked 20 cigarettes or more per day	1332	14.7	372	3.5
Total	9062		10,698	

Table 2 shows the data used in the modeling. It presents the twin and co-twin status in four zygosity groups, according to age at initiation and amount smoked (upper part of the table) or by age at initiation and smoking cessation (lower part of the table).

The correlations of the three variables of age at initiation (continuous), amount smoked (all categories) and smoking cessation are shown in Table 3 for pairs concordant for ever smoking. MZ correlations were higher compared with DZ correlations among both men and women for all traits.

Table 2

Twin Pair Smoking Cessation for Age at Initiation of Smoking (≤ 18 Yrs, 18+, Never), Amount Smoked per Day (< 20 vs. 20+ Cigarettes/Day) and Smoking Cessation (Former, Current, Never), in the 1981 Questionnaire Survey, for Complete Pairs Born Before 1958

Twin status		Co-twin status		Number of pairs			
Age at initiation	Amount smoked	Age at initiation	Amount smoked	MZM	DZM	MZF	DZF
—	N	—	N	350	578	958	1679
≤ 18	< 20	≤ 18	< 20	161	239	169	276
—	N	> 18	> 18	102	287	165	348
≤ 18	≥ 20	≤ 18	≥ 20	80	138	10	20
> 18	< 20	> 18	< 20	80	136	89	119
≤ 18	≥ 20	≤ 18	< 20	60	117	18	27
—	N	≤ 18	< 20	59	274	64	265
≤ 18	< 20	≤ 18	≥ 20	55	150	20	38
≤ 18	< 20	> 18	< 20	42	96	44	78
> 18	< 20	≤ 18	< 20	36	85	27	73
—	N	> 18	≥ 20	31	113	14	54
—	N	≤ 18	≥ 20	30	169	9	42
> 18	≥ 20	> 18	≥ 20	26	54	3	5
> 18	< 20	> 18	≥ 20	21	36	5	14
> 18	≥ 20	> 18	< 20	20	36	6	15
≤ 18	≥ 20	> 18	≥ 20	19	37	4	3
≤ 18	≥ 20	> 18	< 20	17	46	4	11
> 18	< 20	≤ 18	≥ 20	17	51	11	11
> 18	≥ 20	≤ 18	< 20	15	33	0	5
> 18	≥ 20	≤ 18	≥ 20	12	35	4	2
≤ 18	< 20	> 18	≥ 20	11	33	4	8
Age at initiation	Smoking cessation	Age at initiation	Smoking cessation	MZM	DZM	MZF	DZF
—	N	—	N	350	578	958	1679
≤ 18	C	≤ 18	C	175	278	90	150
≤ 18	F	≤ 18	C	107	251	78	144
≤ 18	F	≤ 18	F	87	133	60	80
—	N	> 18	F	82	194	86	215
> 18	F	> 18	F	56	87	34	31
—	N	> 18	C	53	215	101	289
> 18	C	> 18	C	51	79	48	63
—	N	≤ 18	F	46	198	45	156
> 18	F	> 18	C	43	107	23	67
—	N	≤ 18	C	43	250	31	153
≤ 18	F	> 18	C	37	96	29	51
≤ 18	C	> 18	C	34	75	21	33
> 18	C	≤ 18	C	33	96	30	32
> 18	F	≤ 18	C	24	72	9	34
> 18	F	≤ 18	F	23	42	8	25
≤ 18	F	> 18	F	20	46	8	19

Note: ≤ 18 = Age at initiation of smoking ≤ 18 yrs; > 18 = age at initiation of smoking older than 18 yrs; — = never smoked regularly; < 20 = smoked less than 20 cigarettes per day; ≥ 20 = smoked 20 cigarettes or more per day; N = never smoked regularly; F = former smoker; C = current smoker; MZM = male monozygotic pair; DZM = male dizygotic pair; MZF = female monozygotic pair; DZF = female dizygotic pair.

Univariate Modeling

We started the modeling by univariate modeling with continuous variables of age at initiation and amount smoked. Heritability estimate of amount smoked was .49 (95% confidence interval [CI] .44–.54) among men and .52 (95% CI .46–.57) among women. Heritability estimate of age at initiation among men was .36 (95% CI .21–.51) and among women .67 (95% CI .60–.72).

Modeling of Initiation and Amount Smoked

We continued modeling by two-stage analyses of categorized variables of age at initiation and amount

Table 3

The Intrapair Correlations and Confidence Intervals (and Prevalence) for Age at Initiation, Amount Smoked and Smoking Cessation Among MZ and DZ Twin Pairs and Sex Among Ever-Smoker Pairs

	Men		Women	
	MZ	DZ	MZ	DZ
Age at initiation (years)	.49	.34	.55	.36
	.43, .55	.29, .39	.48, .61	.30, .42
	(695)	(1385)	(441)	(747)
Amount smoked	.45	.27	.50	.29
	.39, .51	.22, .32	.43, .57	.22, .36
	(676)	(1343)	(426)	(714)
Cessation (former in 1981)	.56	.31	.50	.25
	.51, .61	.26, .36	.43, .57	.18, .32
	(695)	(1389)	(445)	(738)

smoked. When compared to the full ACE model, the most parsimonious model among men included ACE effects for age at initiation, AE effects for amount smoked and the correlation between the two additive genetic components ($\Delta\chi^2$ = 4.526, p = .21, Δdf = 3). Among women two models offered adequate fit: (1) ACE effects for age at initiation, AE effects for amount smoked and the correlations between the additive genetic and unique environmental factors ($\Delta\chi^2$ = 4.613, p = .100, Δdf = 2); and (2) ACE effects for age at initiation, CE effects for amount smoked and the correlations between the common and unique environmental factors ($\Delta\chi^2$ = 1.548, p = .461, Δdf = 2). Thus, for amount smoked both AE and CE submodels offered adequate fit. In the subsequent modeling, we fitted both of these models for women.

Table 4 shows the estimated genetic and environmental variances and correlations with their 95% confidence intervals in the full ACE two-stage bivariate model and in the most parsimonious models described above. In the best fitting model among men, additive genetic variance was .59 (95% CI .49–.69) and shared environmental variance .19 (95% CI .10–.27) for age at initiation. In the same model, amount smoked had an estimated additive genetic variance of .54 (95% CI .45–.62). There was only a weak genetic correlation between age at initiation and amount smoked (r_a = –.22, 95% CI –.28, –.15).

Among women the estimate for the effect of additive genetic factors was .36 (95% CI .28–.43) and for shared environmental factors .50 (95% CI .43–.57) of the variation of age at initiation. Under the AE model for amount smoked, additive genetic variance was .61 (95% CI .46–.70). Both the additive genetic correlation (r_a = .17, 95% CI –.23, –.04) and the nonshared environmental correlation (r_e = –.04, 95% CI –.09, –.01) between age at initiation and amount smoked were weak. In the CE model for amount smoked, shared environmental variance was .47 (95% CI .36–.58). The shared environmental correlation in the CE model among women between age at initiation and amount smoked was –.15 (95% CI –.24, –.05) and that between unique environmental factors –.07 (95% CI –.13, –.02).

Modeling of Age at Initiation and Smoking Cessation

We continued the analyses by conducting the corresponding modeling for age at initiation and smoking cessation. Compared to the full ACE model, the most parsimonious model included ACE effects for age at initiation, AE effects for smoking cessation and the correlations between additive genetic and unique environmental factors ($\Delta\chi^2$ = 2.772, p = .250, Δdf = 2). Among women the best model included ACE effects for age at initiation, AE effects for amount smoked and the correlation between the unique environmental factors ($\Delta\chi^2$ = .229, p = .973, Δdf = 3).

Table 5 shows the estimated genetic and environmental variances and correlations with their 95% confidence intervals under a two-stage bivariate genetic model for age at initiation and smoking cessation. In the best fitting model among men, additive genetic variance was .59 (95% CI .49–.68) and shared environmental variance was .19 (95% CI .11–.28) for age at initiation. In the same model, smoking cessation had an estimated additive genetic variance of .58 (95% CI .50–.65). There was only a weak additive genetic correlation (r_a = .22, 95% CI .16, .29) and only a weak unique environmental correlation (r_e = –.08, 95% CI –.12, –.04).

The best model for smoking cessation among women was an AE model. Age at initiation had an estimate of additive genetic variance of .34 (95% CI .28–.42) and of shared environmental variance of .51 (95% CI .45–.58). For smoking cessation, additive genetic variance was .50 (95% CI .39–.60). Phenotypic correlation in the AE model among women between age at initiation and smoking cessation was explained only a little by unique environmental factors (r_e = –.13, 95% CI –.15, –.08), and no significant genetic correlation was found.

We also tested the parameters estimates for men and women in the two stage models by equating the parameters and assessing the change in model fit. Models for both age at initiation and amount smoked ($\Delta\chi^2$ = 71.227, p < .001, Δdf = 9) and also age at initiation and smoking cessation ($\Delta\chi^2$ = 89.933, p < .001, Δdf = 9) showed a highly significant difference between men and women.

Discussion

In the present study, we found a strong genetic influence for age at initiation, amount smoked and smoking cessation. These findings are in accordance with results of previous quantitative genetic studies on smoking initiation and cessation (Heath et al., 2002; Li et al., 2003; Madden et al., 2004; Maes et al., 2004) and amount smoked (Vink et al., 2004).

We found in this study that for men the heritability estimate for age at initiation was .59 and for women

Table 4

Proportion of the Variation with 95% Confidence Intervals of Age at Initiation (≤18 Yrs, 18+ Yrs or Never) and Amount Smoked (< 20 vs. 20+ Cigarettes/Day) Accounted for Genetic and Environmental Factors and the Correlations Between These Effects Under a Two-Stage Bivariate Model

	Additive genetic variance	95% CI	Shared environmental variance	95% CI	Unique environmental variance	95% CI
Men						
ACE model for both age at initiation and amount smoked						
Age at initiation	.59	.49, .69	.19	.11, .28	.22	.19, .25
Amount smoked	.32	.06, .57	.17	.0, .36	.51	.41, .61
Genetic–environmental correlation	–.14	–.28, .01	–.06	–.17, .04	–.03	–.08, .03
ACE model forage at initiation and AE model for amount smoked (best model)						
Age at initiation	.59	.49, .69	.19	.10, .27	.22	.19, .25
Amount smoked	.54	.45, .62	—	—	.46	.38, .55
Genetic–environmental correlation	–.22	–.28, –.15	—	—	—	—
Women						
ACE model for both age at initiation and amount smoked						
Age at initiation	.35	.28, .43	.51	.44, .57	.14	.12, .17
Amount smoked	.26	.00, .66	.29	.00, .56	.45	.30, .62
Genetic–environmental correlation	–.06	–.24, .12	–.11	–.25, –.03	–.06	–.13, –.01
ACE model for age at initiation and AE model for amount smoked (best model)						
Age at initiation	.36	.28, .43	.50	.43, .57	.14	.12, .17
Amount smoked	.61	.46, .70	—	—	.39	.30, .54
Genetic–environmental correlation	–.17	–.23, –.04	—	—	–.04	–.09, –.01
ACE model for age at initiation and CE model for amount smoked (best model)						
Age at initiation	.35	.28, .43	.51	.44, .57	.14	.12, .17
Amount smoked	—	—	.47	.36, .58	.53	.42, .64
Genetic–environmental correlation	—	—	–.15	–.24, –.05	–.07	–.13, –.02

Note: The full ACE model and the best models presented.

.34–.36. These estimates are at the same level as the estimates found in the previous studies in which the heritability estimates ranged from .32 to .78 (Edwards et al., 1995; Heath et al., 1993; Heath et al., 1999; Heath et al., 1998; Kendler et al., 1999; Madden et al., 1999; Madden et al., 2004; True et al., 1997; Vink, 2004). However, in contrast to previous studies (Li et al., 2003; Madden et al., 1999), we found that the heritability of smoking initiation appears to be higher among men than among women. This sex difference may, however, be associated with different definitions of smoking initiation. In our study, age at initiation was classified as early initiation, late initiation and no initiation to smoke, whereas in many previous studies initiation was dichotomized as ever or never smoked.

When studying amount smoked, we found the heritability estimates of .54 for men and .61 for women. Previous quantitative genetic studies on amount smoked have been done mostly among men (Carmelli et al., 1990; Swan et al., 1996; Swan et al., 1997; Swan et al., 1990; Vink et al., 2004), and the heritability estimates in these studies were at the same level than in our study. In a previous study where both men and women were included (Vink et al., 2004) heritability estimates were also at the same level than in the present study. The study of adolescent and young adults of Koopmans and her colleagues (Koopmans et al., 1999) were reported higher heritability estimates (.86, 95% CI .70–.94) of amount smoked.

The heritability estimate for smoking cessation was .58 among men and .50 among women. In the previous studies, where only a few include both men and women from the same population, heritability estimates of smoking cessation have varied from .11 to .74 (Heath et al., 1993; Heath et al., 1999; Heath et al., 1998; Heath et al., 2002; Kaprio et al., 1981; Kendler et al., 2000; Madden et al., 1999; Medlund et al., 1977; True et al., 1997). Previous studies show that genetic effects on smoking cessation is higher among men than among women (Li et al., 2003; Madden et al., 2004; Maes et al., 2004). We found a

Table 5

Proportion of the Variation With 95% Confidence Intervals of Age at Initiation (≤ 18 Yrs, 18+ Yrs or Never) and Smoking Cessation (Former vs. Current Smoker) Accounted for Genetic and Environmental Factors and the Correlations Between These Effects Under a Two-Stage Bivariate Model

	Additive genetic variance	95% CI	Shared environmental variance	95% CI	Unique environmental variance	95% CI
Men						
ACE model for both age at initiation and smoking cessation						
Age at initiation	.59	.49, .68	.19	.11, .25	.22	.19, .26
Smoking cessation	.45	.21, .64	.10	.00, .26	.45	.36, .54
Genetic–environmental correlation	.23	.16, .29	—	—	–.09	–.13, –.04
ACE model for age at initiation and AE model for smoking cessation (best model)						
Age at initiation	.59	.49, .68	.19	.11, .28	.22	.19, .25
Smoking cessation	.58	.50, .65	—	—	.43	.35, .50
Genetic–environmental correlation	.22	.16, .29	—	—	–.08	–.12, –.04
Women						
ACE model for both age at initiation and smoking cessation						
Age at initiation	.34	.27, .42	.51	.45, .58	.15	.12, .17
Smoking cessation	.50	.19, .60	.00	.00, .23	.50	.40, .63
Genetic–environmental correlation	—	—	–.00	–.10, .06	–.13	–.17, –.08
ACE model for age at initiation and AE-model for smoking cessation (best model)						
Age at initiation	.34	.28, .42	.51	.45, .58	.15	.12, .17
Smoking cessation	.50	.39, .60	—	—	.50	.40, .61
Genetic–environmental correlation	—	—	—	—	–.13	–.15, –.08

Note: The full ACE model and the best models presented.

similar sex difference in this study as well, but it was not very large.

The trait correlation between age at initiation and amount smoked in men was explained solely by the genetic correlation (r_a = –.22). A similar genetic correlation was found also for age at initiation and smoking cessation (r_a = .22). Thus, there are partly the same genes to predispose these traits, but this proportion is not large. These correlations suggest that genetic influences to age at initiation accounted for at most about 4% of the genetic factors in amount smoked or in smoking cessation. In the study of Heath and his colleagues (2002) on age at initiation and smoking cessation, a weak and statistically nonsignificant genetic correlation was found in men (r_a = .11). In the present study, the genetic correlation between age at initiation and amount smoked among women was .17 if the AE model was used, indicating that genetic influences on initiation accounted for about 2% of the genetic factors in amount smoked. In the study of Heath and his colleagues (2002), the correlation was somewhat higher (r_a = .28) in women, but still account for less than 8%. In the present study, environmental correlation was weak or did not exist among men and women in age at initiation and amount smoked or smoking cessation. We also found that age at initiation and smoked cigarettes per day as well as initiation and smoking cessation might share some genetic factors. This would suggest that linkage analyses could identify such common genes. Vink and her colleagues (2004) showed in Dutch linkage analysis that on chromosome 10 there was a peak in the same region for both number of cigarettes and smoking initiation traits, but the specific genes are not yet known. However, it is likely that in the most part different genes will be responsible for the liability to smoking initiation and to the ability to quit smoking or amount smoked. Thus, careful phenotypic assessment of subjects in linkage and association studies is needed.

Our study has several important strengths. Our study population is large, which gives adequate power to study not only of smoking behavioral traits but also the associations between these traits. Earlier studies have used smaller number of twin pairs with a notable exception of the study of Madden and her colleagues (2004), which used pooled twin data from Australian, the United States and Finland. The data come from retrospective self-reports of age at initiation of substance abuse. Self-reported data on substance use, particularly age at initiation, can be unreliable (Johnson & Mott, 2001). However in our data, age at

initiation was found to be quite reliable: the correlation between age at initiation as reported in 1975 and 1981 health questionnaires was high and did not vary by smoking status or sex (r = .84 among all smokers). The strength of the present study is also that we had both men and women in our data whereas many previous studies were targeted to men only. We have only limited information on smoking behavior based on self-report, and we do not have, for example, any measure of nicotine dependence. Another limitation of our study is that our data do not include opposite-sex twin pairs, and thus we are not able to examine sex-limitation effects in the heritability of smoking behavior.

In conclusion, the present results confirmed that genetic factors are important in amount smoked and smoking cessation and these genetic factors are largely independent of genetic influences on age at initiation. This has implications for defining phenotypes in searches for genes underlying smoking behaviors.

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References

American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed., rev.). Washington, DC: Author.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Boomsma, D., Busjahn, A., & Peltonen, L. (2002). Classical twin studies and beyond. *Nature Reviews Genetics*, *3*, 872–882.

Broms, U., Silventoinen, K., Lahelma, E., Koskenvuo, M., & Kaprio, J. (2004). Smoking cessation by socioeconomic status and marital status: The contribution of smoking behavior and family background. *Nicotine & Tobacco Research*, *6*, 447–455.

Carmelli, D., Swan, G. E., Robinette, D., & Fabsitz, R. R. (1990). Heritability of substance use in the NAS-NRC Twin Registry. *Acta Geneticae Medicae et Gemellologiae*, *39*, 91–98.

Edwards, K. L., Austin, M. A., & Jarvik, G. P. (1995). Evidence for genetic influences on smoking adult women twins. *Clinical Genetics*, *47*, 236–244.

Heath, A. C., Cates, R., Martin, N. G., Meyer, J. M., Hewitt, J. K., Neale, M. C., & Eaves, L. J. (1993). Genetic contribution to risk of smoking initiation: Comparisons across birth cohorts and across cultures. *Journal of Substance Abuse*, *5*, 221–246.

Heath, A. C., Kirk, K. M., Meyer, J. M., & Martin, N. G. (1999). Genetic and social determinants of initiation and age at onset of smoking in Australian twins. *Behavior Genetics*, *29*, 395–407.

Heath, A. C., Madden, P. A., & Martin, N. G. (1998). Statistical methods in genetic research on smoking. *Statistical Methods in Medical Research*, *7*, 165–186.

Heath, A. C., Martin, N. G., Lynskey, M. T., Todorov, A. A., & Madden, P. A. F. (2002). Estimating two-stage models for genetic influences on alcohol, tobacco or drug use initiation and dependence vulnerability in twin and family data. *Twin Research*, *5*, 113–124.

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerström, K.-O. (1991). The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. *British Journal of Addiction*, *86*, 1119–1127.

Jarvis, M. J. (2004, October). *The behavioural epidemiology of nicotine dependence: What we know, and some of the gaps*. Paper presented at the 6th Annual Conference of the SRNT (Society for Research on Nicotine and Tobacco) Europe, Tübingen, Germany.

Johnson, T. P., & Mott, J. A. (2001). The reliability of self-reported age of onset of tobacco, alcohol and illicit drug use. *Addiction*, *96*, 1187–1198.

Kaprio, J., & Koskenvuo, M. (1988). A prospective study of psychological and socioeconomic characteristics, health behavior and morbidity in cigarette smokers prior to quitting compared to persistent smokers and non-smokers. *Journal of Clinical Epidemiology*, *41*, 139–150.

Kaprio, J., & Koskenvuo, M. (2002). Genetic and environmental factors in complex diseases. *Twin Research*, *5*, 358–365.

Kaprio, J., Koskenvuo, M., & Sarna, S. (1981). Cigarette smoking, use of alcohol, and leisure-time physical activity among same-sexed adult male twins. *Progress in Clinical and Biological Research*, *3*, 37–46.

Kendler, K. S., Neale, M. C., Sullivan, P., Corey, L. A., Gardner, C. O., & Prescott, C. A. (1999). A population-based twin study in women of smoking initiation and nicotine dependence. *Psychological Medicine*, *29*, 299–308.

Kendler, K. S., Thornton, L. M., & Pedersen, N. L. (2000). Tobacco consumption in Swedish twins reared apart and reared together. *Archives of General Psychiatry*, *57*, 886–892.

Koopmans, J. R., Slutske, W. S., Heath, A. C., Neale, M. C., & Boomsma, D. I. (1999). The genetics of smoking initiation and quantity smoked in Dutch adolescent and young adult twins. *Behavior Genetics*, *29*, 383–393.

Lessov, C. N., Martin, N. G., Statham, D. J., Todorov, A. A., Slutske, W. S., Bucholz, K. K., Heath, A. C., & Madden, P. A. (2004). Defining nicotine dependence for genetic research: Evidence from Australian twins. *Psychological Medicine*, *34*, 865–879.

Li, M. D., Cheng, R., Ma, J. Z., & Swan, G. E. (2003). A meta-analysis of estimated genetic and environmental

effects on smoking behavior in male and female adult twins. *Addiction*, *98*, 23–32.

Madden, P. A. F., Heath, A. C., Pedersen, N. L., Kaprio, J., Koskenvuo, M., & Martin, N. G. (1999). The genetics of smoking persistence in men and women: A multicultural study. *Behavior Genetics*, *29*, 423–431.

Madden, P. A. F., Pedersen, N. L., Kaprio, J., Koskenvuo, M. J., & Martin, N. G. (2004). The epidemiology and genetics of smoking initiation and persistence: Crosscultural comparisons of twin study results. *Twin Research*, *7*, 82–97.

Maes, H. H., Sullivan, P. F., Bulik, C. M., Neale, M. C., Prescott, C. A., Eaves, L. J., & Kendler, K. S. (2004). A twin study of genetic and environmental influences on tobacco initiation, regular tobacco use and nicotine dependence. *Psychological Medicine*, *34*, 1251–1261.

Medlund, P., Cederlof, R., Floderus-Myrhed, R., Friberg, L., & Sørensen, S. (1977). A new Swedish Twin Registry. *Acta Medicae Scandinavica Supplementum 600*.

Neale, M. C., Boker, S. M., Xie, G., & Maes, H. H. (2003). *Mx: Statistical modeling* (6th ed.). Richmond, VA: Department of Psychiatry, Medical College of Virginia.

Posthuma, D., Beem, A. L., de Geus, E. J. C., van Baal, G. C. M., von Hjelmborg, J. B., Iachine, I., & Boomsma, D. I. (2003). Theory and practice in quantitative genetics. *Twin Research*, *6*, 361–376.

Sarna, S., Kaprio, J., Sistonen, P., & Koskenvuo, M. (1978). Diagnosis of twin zygosity by mailed questionnaire. *Human Heredity*, *28*, 154–161.

Swan, G. E., Carmelli, D., & Cardon, L. R. (1996). The consumption of tobacco, alcohol, and coffee in Caucasian male twins: A multivariate genetic analysis. *Journal of Substance Abuse*, *8*, 19–31.

Swan, G. E., Carmelli, D., & Cardon, L. R. (1997). Heavy consumption of cigarettes, alcohol and coffee in male twins. *Journal of Studies on Alcohol*, *58*, 182–190.

Swan, G. E., Carmelli, D., Rosenman, R. H., Fabsitz, R. R., & Christian, J. C. (1990). Smoking and alcohol consumption in adult male twins: Genetic heritability and shared environmental influences. *Journal of Substance Abuse*, *2*, 39–50.

True, W. R., Heath, A. C., Scherrer, J. F., Waterman, B., Goldberg, J., Lin, N., Eisen, S. A., Lyons, M. J., & Tsuang, M. T. (1997). Genetic and environmental contributions to smoking. *Addiction*, *92*, 1277–1287.

True, W. R., Xian, H., Scherrer, J. F., Madden, P. A. F., Bucholz, K. K., Heath, A. C., Eisen, S. A., Lyons, M. J., Goldberg, J., & Tsuang, M. (1999). Common genetic vulnerability for nicotine and alcohol dependence in men. *Archives of General Psychiatry*, *56*, 655–661.

Vink, J. M. (2004). *A twin-family study of smoking behavior*. Amsterdam, the Netherlands: Vrije Universiteit.

Vink, J. M., Beem, A. L., Posthuma, D., Neale, M. C., Willemsen, G., Kendler, K. S., Slagboom, P. E., & Boomsma, D. I. (2004). Linkage analysis of smoking initiation and quantity in Dutch sibling pairs. *The Pharmacogenomics Journal*, *4*, 274–282.